AWARD NUMBER: W81XWH-14-1-0373

TITLE: Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury

PRINCIPAL INVESTIGATOR: Philip C. Spinella, MD

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St. Louis, MO 63110

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our major accomplishments during the third year of the study include attainment of FDA IND renewal approval, successful execution and completion of training all study team members for the clinical, data collection/entry, and laboratory procedures for the trial. We obtained WU IRB and DoD HRPO continuing approval of the study. The DSMB continued to meet quarterly to review safety data for study participants. Finally, we enrolled 100% of the expected total enrollment of 150 patients. PK and PK sample analyses have been performed on 100 participants and the immunology, PK, and data analyses are currently under way.

15. SUBJECT TERMS

Trauma, hemorrhage, transfusion, fibrinolysis, immune suppression, pharmacokinetics, outcomes, adverse events.

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Title: Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury

(TAMPITI Trial)

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Award Number: W81XWH-14-1-0373
Log Number: 13335005

Philip C. Spinella, MD
Grant V. Bochicchio, MD, MPH

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1. INTRODUCTION:

This single center randomized controlled trial in adult patients with severe traumatic injury will determine if the use of tranexamic acid within 2 hours of injury is associated with less immune suppression compared to placebo. Tranexamic acid doses of 4g and 2g will be analyzed. In addition the pharmacokinetics of tranexamic acid will be established in addition to outcome and safety measures. We will also develop a biorepository of plasma samples for future analysis of coagulation and endothelial injury parameters.

2. KEYWORDS:

Trauma, hemorrhage, transfusion, fibrinolysis, immune suppression, pharmacokinetics, outcomes, adverse events.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Task 1: Obtain FDA IND and Community Consent for trial. (Timeframe: 1-6 months).

FDA IND initial approval was received 20-FEB-2015 (letter received 19-MAY-2015)

- Community Consultation Activities took place between 28-MAR-2015 and 18-MAY-2015 and the results of the activities were reported to the WU IRB and were reviewed by a full board on 23-SEP-2015. WU IRB approval was received 16-OCT-2015.
- WU IRB review and approval was contingent on the Barnes Jewish Hospital Emergency Medicine Research Committee's approval which had been previously granted on 09-APR-2015.

- Secretary of the Army Approval was granted on 11-SEP-2015.
- Public Disclosure activities began 22-OCT-2015 and are planned to continue throughout the performance of this trial.

Task 2: Conduct a multi-center, double-blinded, Randomized Controlled Trial (RCT) of 150 patients with three study groups; TXA 2 gram IV bolus, TXA 4 gram IV bolus, and placebo. (Timeframe: months 7-32).

Enrollment began 01- MAR-2016 after completing Public Disclosure activities to the satisfaction of the Washington University IRB. We completed enrollment of all study participants (150 total participants) on July 2nd, 2017 and are currently working on the immunology, pharmacokinetic, and data analysis. Once we have analyzed all samples and data, we will disseminate the information to the public via public disclosure efforts. We expect the project to be completed by September 14, 2018.

What was accomplished under these goals?

Our major accomplishments during the third year of the study include attainment of FDA IND renewal approval, successful execution and completion of training all study team members for the clinical, data collection/entry, and laboratory procedures for the trial. We obtained WU IRB and DoD HRPO continuing approval of the study. The DSMB continued to meet quarterly to review safety data for study participants. Finally, we enrolled 100% of the expected total

enrollment of 150 patients. PK and PD sample analyses have been performed on 100 participants and the immunology, PK, and data analyses are currently under way.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

We continue to provide further information to the community regarding the investigation, risk and benefits, and information pertaining to the exception from informed consent for emergency research through public disclosure efforts. We have utilized local, and regional broadcasting, newspapers, town hall meetings, as well as posters and signage.

In addition, our website remains active but has been updated to reflect enrollment completion. Research team members continue to promptly answer questions posed on-line about the study a. Clinicaltrials.gov has also been updated to reflect enrollment completion. Finally, a public disclosure plan is currently being drafted to provide a comprehensive and robust effort to share the results of our study.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period we plan to complete PK, immunology, and data analysis, as well as manuscript preparation

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  There have been formal (power point presentation at a variety of organized community meetings in addition to a presentation to the Barnes Jewish Hospital Emergency Medicine Research Committee) and informal presentations made to the community as part of our community consultation and public disclosure efforts. In addition, members of the DSMB have been presented interim data during their quarterly meetings.

  Journal publications.

  Nothing to Report

  Books or other non-periodical, one-time publications.

  Nothing to Report

  Other publications, conference papers, and presentations.

  Nothing to Report

- **Website(s) or other Internet site(s)**
  www.tampiti.wustl.edu
    - Our website provides detailed information regarding the study (Investigators, design, sponsor, the problem, purpose, etc). The website also provides links to "opt out forms", "request information forms", contact information for the study team, links to our Facebook and Twitter pages, feedback forms, our community power point presentation, and the NIH video explaining emergency research and the EFIC, in addition to relevant references supporting the purpose of this study.

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**

  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Philip C. Spinella, MD
Project Role:	PI
Research Identifier	ORCID ID: 0000-0003-1721-0541
Nearest person month worked	1
Contribution to Project:	Dr. Spinella has led the protocol and methods development for this trial in addition to the FDA IND renewal submission. He assisted with several community consultation activities, conferred with the WU HRPO leadership to continue the successful execution of this trial. Dr. Spinella assists with the oversight of the study, reviewing AEs/SAEs, DSMB reports, and data collection/entry questions.
Funding Support:	During the reporting period, Dr. Spinella has received funding support from NIH/NHLBI (UO1HL072268, U01HL116383, R21HL128863), Children's Discovery Institute (CDI-EI-2015-499), DoD (W81XWH-13-C-0160, WX81XWH-14-1-0373, N00014-13-C-0260), American Heart Association(16GRANT31180018), CERUS Corporation (CLI00112), and Octapharma Plasma Inc (LAS212, LAS213).

Name:	Grant V. Bochicchio, MD, MPH
Project Role:	Co-PI
Research Identifier:	ORCID ID: 0000-0002-8313-1449
Nearest person month worked	1
Contribution to Project:	Dr. Bochicchio has assisted with protocol modifications, FDA IND renewal submission, and has worked with the study team and WU IRB Leadership for guidance and developing processes and procedures for unplanned enrollment of prisoners and minors. He has participated in and has led several community consultation and public disclosure activities. Dr. Bochicchio has met with

	key stakeholders regarding this project (including the Emergency Medicine Leadership, HRPO leadership, Trauma Surgery Faculty, Ortho Spine Faculty, Trauma Anesthesia Faculty, etc.) and continues to oversee study execution logistics and patient safety.
Funding Support:	During the reporting period, Dr. Bochicchio had funding support from, NIH- KaloCyte (R42HL135965, R21HD086784-01A1), Foundation for Barnes -Jewish Hospital, and DoD (W81XWH-14-1-0373, DM140394, W81XWH1510504).

Name:	Kelly Bochicchio, RN, MS
Project Role:	Clinical Research Specialist
Research Identifier	unknown
Nearest person month worked	3
Contribution to Project:	Ms. Bochicchio has functioned as the overall project manager for this trial. She has prepared all regulatory documents for submission, review, and approval to the WU IRB and DoD HRPO. She assisted with the FDA IND renewal submission and organized and led the Community Consultation and Public Disclosure Plan activities. She has trained the research team regarding data collection and entry, and all study related procedures. She is responsible for the overall research team management.
Funding Support:	During the reporting period, Ms. Bochicchio had funding support from NIH (5R44HL08629305) and the Department of Defense (W81XWH1210550, W81XWH-14-0373).

Name:	Anja Fuchs
Project Role:	Co-Investigator
Research Identifier	ORCID ID: 0000-0002-0186-4308
Nearest person month worked	1
Contribution to Project:	Dr. Fuchs has developed and validated laboratory techniques associated with the cytokine and PK/PD procedures being performed for this trial. During this reporting period, she had trained all study staff regarding bench SOPs for laboratory work and has begun to analyze patient samples.
Funding Support:	During the reporting period, Dr. Fuchs had funding support from NIH (1R25NS09098501), the DoD W81XWH-14-1-0373), and The Foundation for Barnes-Jewish Hospital.

Name:	Avril Adelman
Project Role:	Biostatistician
Research Identifier	unknown
Nearest person month worked	1
Contribution to Project:	Ms. Adelman has finalized the case report form and RedCap database for this trial. She has run reports for the DSMB and has prepared reports for the FDA IND renewal, developing case report forms and the database for this trial. In addition, she has assisted with deciding the randomization plan and reports to be presented to the DSMB.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS:

None

9. APPENDICES:

None